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Article

Appreciation for analysis of how levonorgestrel works and reservations with the use of meloxicam as emergency contraception

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This paper is a response to Dr. Kathleen Raviele's recent article on her critical analysis of the use of levonorgestrel given to women postsexual assault and her suggestion that the use of Meloxicam may be an ethical alternative.

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Dr. Kathleen Raviele has written an important, and needed, review ("Levonorgestrel in cases of rape: How does it work?") that adds to the growing body of evidence demonstrating postfertilization (abortifacient) actions of the so-called emergency contraception (EC), Plan B/Plan B One-Step (levonorgestrel, LNG) (Raviele 2014). In fact, we will discuss five examples of such LNG postfertilization effects. Our reservations are not with the paper's conclusions relative to the ethical impermissibility of Plan B, Raviele's paper's primary focus. In fact, we gratefully applaud her paper that includes expert analyses of the Durand and Noé reports[1] (Durand et al. 2001; Noé et al. 2010). Moreover, her responses to Reznik and Hamel of the Catholic Health Association are masterful (Hamel 2010; Reznik 2010; Raviele 2014).

As noted by Raviele, Durand et al. (2001) studied 45 sterilized women, and the effect on ovulation that was produced by oral LNG given on various cycle days. The initial study design was to give LNG (0.75 mg × 2) to groups A, B, and C (on "day 10," the day of the luteinizing hormone [LH] surge, and day LH+2, respectively). However, because of poor correlation between the patients' performed home urinary LH testing and subsequent researcher/laboratory serum LH values, a post-study reassignment of

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eight subjects (four subjects each from groups B and C) into a new late follicular phase group D was done by Durand et al.

All 30 women in groups B, C, and D (i.e., women given LNG within 3 days of the LH surge or later) ovulated. Nonetheless, 12 of 15 (80%) of the women in group A did *not* ovulate, but Raviele is on target when she notes, "Timing is everything!" She concludes that "day 10" in group A is "day −5 or earlier" (Raviele 2014, 121). In fact, our analysis of Durand's Table 2 leads us to conclude that "day 10" (group A) was given LNG on day −8, clearly before the 6-day fertile window (days −5 to 0).[2] Thus, this demonstrated pre-ovulatory effect could not account for any of the LNG-EC effectiveness, as no pregnancies would be expected on day −8.

A close look at Durand et al.'s group D is also quite informative. Raviele is right that these reassigned participants received "LNG-EC within 3 days of the onset of the LH surge (i.e., days −4 to −2) [and] all ovulated." She further correctly observes that, "Progesterone production was found to be deficient." In fact, the integrated luteal serum progesterone area under the curve ("ILP_4-AUC") was reduced 82 percent in these subjects (i.e., 90.3 ng/ml in controls to 15.9 in Group D, $P < 0.05$). Raviele further surmises, "there was a shorter luteal phase, which would interfere with implantation" (Raviele 2014, 121). Thus, LNG induced a marked reduction in luteal phase progesterone, as well as a shortening of the luteal phase. Both of these findings are clear examples (examples 1 and 2) of postfertilization effects.

Hence, Durand et al. demonstrated that LNG did not prevent ovulation in these 45 patients, unless it was given before day −7 (i.e., day −8), and the ovulation prevention in these 12 of the 15 subjects in group A was clearly outside the fertility window. The FDA has stated that Plan B is 89 percent effective in the prevention of expected clinical pregnancies (PDR 2005, s.v. "Plan B, Barr Laboratories, Inc.," 779–781). Moreover, Russian researchers reported precisely this same "[i]nterceptive" efficacy in baboons (Oettel et al. 1980). This is the third example of a Plan B postfertilization effect. The probability of pregnancy on day −8 (or earlier) approximates zero. Therefore LNG given on day −8 (or earlier), could maximally account for essentially 0 percent of the attributable Plan B "preventive" efficacy rate of 89 percent, irrespective of whether ovulation was prevented, delayed, or unchanged.

Moreover, Novikova et al. also published a report on the action of LNG given to 99 women (Novikova et al. 2007, with co-author Croxatto). Their Table 1 shows that among the 51 women who had unprotected intercourse in the fertile window, only 7 received the hormone earlier than day −4 (i.e., day −5 with probability of pregnancy of only 0.04) (Wilcox, Weinberg, and Baird 1998). As noted in their Table 1, these researchers, given the low fertility rate of day −5, expected only 0.28 pregnancies from these seven women (i.e., $7 \times 0.04 = 0.28$). Thus, the maximum proportion of prevented clinical pregnancies that could be attributed to an LNG-induced prevention of ovulation effect was 3.7 percent, as a total of 7.60 pregnancies were expected ($0.28/7.60 = 0.0368$) in this report (Novikova et al. 2007). Stated differently, 96.3 percent of the prevented clinical pregnancies ($1–0.0368$) occurred by other than an ovulation prevention mechanism.

Raviele's analysis of the Noé et al. (2010) study is also very instructive, and is example 4 of a Plan B postfertilization effect. She correctly notes that 62 of the 87 women

who ingested LNG on days –5 to –1 ovulated, as determined by ultrasound (a 71 percent ovulation rate; and up to an 86 percent ovulation rate, if the 15 women who did not attend follow-ups are counted). There were 13 expected pregnancies among these 87 women, but despite documented ovulation, no pregnancies occurred after LNG-EC administration. Raviele insightfully and accurately notes, "This is additional strong evidence that LNG-EC has a post-fertilization effect" (Raviele 2014, 123). This is the same conclusion that Russian baboon researchers had reached 34 years prior.[3]

The Croxatto group had previously claimed that LNG-EC "prevents pregnancy primarily by interference with the ovulatory process" (Croxatto et al. 2004).[4] Noé et al. (including Croxatto himself) make a major subsequent concession: "Despite the evidence of ovulation in these women who took LNG-EC before ovulation occurred, no pregnancies occurred among them. This finding dissuades our doubt with respect to the lack of contraceptive effectiveness of LNG once the LH surge has been initiated" (Noé et al. 2010). Stated plainly, these international EC promoters/researchers are conceding that Plan B, given during the high fertility days just prior to the LH surge and expected ovulation (i.e., day –2 to 0), does not, in fact, usually prevent ovulation. Nonetheless, a clinical pregnancy (a baby) is "prevented."

So, how do these researchers/promoters now claim that LNG has *only* a prefertilization action? It is back to square one, as they now claim, "this suggests that other mechanism than suppression of ovulation prevents pregnancy in these women. We postulate that increased cervical mucus viscosity caused by LNG impedes the migration of sperm" (Noé et al. 2010). Novikova et al. (2007) gave LNG up to 120 hours (!) after unprotected coitus, and the three women who became pregnant, received it 40 hours post-coitus. After reviewing relevant data, Raviele concludes that, "LNG does not impair the quality of cervical mucus or sperm penetration of the cervix or the ability of sperm to fertilize an oocyte" (Raviele 2014, 124).

Sperm can be retrieved from the fallopian tubes within 5 minutes to 2 hours after artificial insemination in the vagina (Peck and Veléz 2013). It is doubtful that sperm arrival at the fallopian tubes would be slower when deposited naturally deep in the vaginal vault during coital ejaculation. How LNG, given 40–120 hours post-coitus, could impede sperm penetration stretches credulity to the limit. EC promoters/researchers Hapangama, Glasier, and Baird (2001) have conceded as much: "However, even if LNG has an effect on cervical mucus, which interferes with sperm penetration, that action is unlikely to prevent pregnancy when taken some 12–72 hr after coitus."

Additionally, Raviele, as well as Peck and Veléz, has extensively reviewed the issue of possible pre-fertilization mechanisms (i.e., LNG-EC effects on cervical mucus, sperm transport, sperm capacitance, and sperm-oocyte binding) (Raviele 2014; Peck and Veléz 2013). Raviele concludes, "Studies on various aspects of sperm function after LNG have not supported this as a mechanism of action" (Raviele 2014, 124). Peck and Veléz (2013) also concluded, "In summary, the totality of scientific evidence shows that LNG-EC has little or no effect on cervical mucus or sperm functions. Its effects on these processes cannot explain its effectiveness in reducing pregnancy risk."

The claim that Plan B (LNG) works exclusively by prefertilization effect(s),

particularly via the prevention of ovulation, is becoming nearly as credible as previous claims by abortion advocates that "life/pregnancy begins at implantation," "OTC-EC will prevent 1,000,000 surgical abortions," or their initial claim (that lost all credibility with the general use of ultrasonography and has quietly disappeared) that "it's just a glob of tissue."[5]

Ultimately, pregnancies surviving so-called EC in the massive WHO trials were uniformly eliminated with surgical abortion, a plan C (Ho and Kwan 1993).[6] This fact is seldom, if ever, discussed by Catholic bioethicists in their defense of LNG-EC for rape. Nor do these reputed ethical experts mention that the multiple and massive WHO levonorgestrel trials were referred to as "post-ovulatory" (Von Hertzen et al. 2002).

Moreover, a head to head comparison of LNG (two 0.75 mg doses or one 1.5 mg dose) versus RU-486 component (mifepristone) has been reported by Von Hertzen et al. In this large WHO trial with more than 4000 participants, there was no significant difference in the three groups. LNG was as effective as mifepristone, but further analysis was quite revealing: "having unprotected intercourse (without contraception) between treatment and expected menstruation resulted in much higher pregnancy rates in the mifepristone group (9/41 [22.0%]) than the levonorgestrel groups (4/61 [6.6%]). In women who did not report having intercourse after treatment, there were 12 pregnancies out of 1318 (0.9%) in the mifepristone group and 40 out of 2651 (1.5%) in the two levonorgestrel groups combined." Mifepristone and LNG are eliminating a large number of early embryos that have resulted from late-in-cycle coitus, and LNG is much more efficient than mifepristone (postfertilization effect example 5; Von Hertzen et al. 2002).

Additionally, we also wish to enumerate the reasons for our reservations with Raviele's two pages of support for an EC "possible alternative," the 5-day usage of the selective non-steroidal anti-inflammatory drug (NSAID)—COX-2 inhibitor—Mobic (meloxicam) (PDR 2000, s.v. Mobic). The risk to the embryo with the usage of meloxicam as EC is real.

(1) *Mobic (meloxicam) pharmacology—important role in implantation.* Implantation is a "very intricate process" that involves "a variety of molecules as potential mediators of embryo-uterine interactions" including cross talk between the blastocyst and the endometrium. Prostaglandins (PGs) are synthesized by the endometrium and the conceptus, and "regulate endometrial function and conceptus implantation" in "mice and humans" (Dorniak, Bazer, and Spencer 2011). The NSAID, meloxicam, blocks an enzyme (type 2 cyclo-oxygenase synthetase) that produces prostaglandins.

There have been multiple reports addressing the important role of prostaglandins in the implantation of the blastocyst (Jabbour and Sales 2004; Kelly, King, and Critchley 2001; Singh, Chaundhry, and Asselin 2011). A review by Singh et al. concludes, "Extensive research in past years provides crucial evidence confirming the role of PGs [prostaglandins] in [the] implantation process" (Singh, Chaundhry, and Asselin 2011). Likewise, a 2012 review of mechanisms of implantation has concluded, "Implantation is considered a proinflammatory reaction, and one early discernible mark is an increased endometrial vascular permeability at the attachment site. Cyclooxygenase (Cox)-derived prostaglandins were shown to mediate these effects" (Cha, Sun, and Dey 2012).

As early as 1978, NSAIDs had been reported to have adverse postfertilization properties (Mendonca et al. 2000;

Yegnanarayan and Joglekar 1978). Researchers Yegnanarayan and Joglekar had concluded that the anti-inflammatory drugs (i.e., aspirin and the NSAIDs) have "an infertility activity in the form of anti-ovulatory, anti-implantation and fetal resorptive properties…on the basis of prostaglandin synthesis inhibition" (Yegnanarayan and Joglekar 1978).

Moreover, in a recent report addressing the safety of NSAID usage by pregnant women with rheumatoid arthritis, Bermas (2014) cites two studies with divergent results, and urges caution ("use should be minimized during the first trimester") due to the adverse effects on ovulation, implantation, and spontaneous abortions (Nakhai-Pour et al. 2011; Edwards et al. 2012). A possible reconciliation of this apparent discrepancy is the fact that Velez Edwards et al. studied over-the-counter NSAIDs, whereas Nakhai-Pour et al. reported on the risk of "spontaneous abortion" associated with prescription strength NSAIDs, which are generally administered at a higher dose. To be (scientifically) precise, a drug-induced abortion is not a "spontaneous abortion," but a medical abortion.

A 2013 NSAID study of macaque monkeys by McCann et al. compared a 5-day meloxicam-EC peri-ovulatory regimen (given at the "the highest dose recommended for humans") that began on the day of a single instance of breeding to controls. There was a 6.5 percent pregnancy rate in the EC group compared to 33.3 percent in the controls — a calculated efficacy rate of 80 percent[7] (McCann et al. 2013). A closer look at this study is informative.

McCann et al. find that meloxicam is a weak inhibitor of ovulation: "[M]eloxicam administration around the time of ovulation likely delays, but does not ultimately prevent cumulus expansion, follicle rupture and oocyte release. The high pregnancy rates in all monthly contraceptive models [75–100%] is clear evidence that oocyte release does typically occur with meloxicam treatment" (McCann et al. 2013). Nonetheless, clinical pregnancies are reduced by 80 percent in this controlled EC monkey trial, and a strong post-ovulatory mechanism of pregnancy termination is apparent as ovulation "typically" occurs.[8]

Beyond the risk of "spontaneous abortions" in primates, another clinical concern is the risk of fetal anomalies from meloxicam, whether it is administered as peri-ovulatory EC or as one of McCann et al.'s three contraceptive models. McCann et al. provide this "reassurance" from their research with non-human primates: "Meloxicam administration extended into the luteal phase in two of the monthly regimens in the present study but did not appear to negatively impact oocyte maturation, fertilization, or implantation as the majority of the animals on these monthly regimens became pregnant." Nonetheless, these researchers reveal that all pregnancies were promptly terminated using an abortion cocktail of mifepristone, misoprostol, and oxytocin "within a week" of pregnancy diagnosis (i.e., during the fourth fetal week or a few days later) (McCann et al. 2013).

Caution is clearly warranted with this "reassurance" by McCann et al. regarding meloxicam's absence of risk. A true assessment of fetal risk is rendered impossible when the early primate life is aborted rapidly ("within a week") and without post-mortem inspection of the fetus being reported (McCann et al. 2013).

(2) *Mobic: animal pharmacology.* Raviele provides two research reports in support of her consideration of Mobic for EC. The former report, a study with mice, found that the first "conspicuous sign of the implantation process" was increased vascular

permeability at the site of the blastocyst attachment. Furthermore, COX-2 deficiency in mice interfered with "ovulation, fertilization, implantation and decidualization" (Lim et al. 1997). More than ovulation prevention was at work.

Raviele summarized the findings of the Lim paper, "Disruption of COX-2 production [as would occur with the partially selective COX-2 inhibiter, meloxicam] causes reproductive failure in mice, including preventing ovulation, fertilization, implantation and decidualization" (Raviele 2014, 127). Prostaglandins are "essential for these processes," state Lim et al., "A 'two-way' interaction between the blastocyst and uterus is essential for successful implantation and subsequent decidualization" (Lim et al. 1997). The disruption of these last two pregnancy-critical processes are abortifacient actions that result in "reproductive failures."

In the same paragraph Raviele then quotes Jesam et al. who found that meloxicam was associated with failure to ovulate or "dysfunctional ovulation." Jesam et al., however, concede that "follicular rupture had occurred in *all* of the treatment cycles by the time of the next menstrual-like period" (Jesam et al. 2010, emphasis added). Raviele then theorizes in this same paragraph, "A non-hormonal drug which targets only ovulation would be licit EC in cases of rape if the intention is to prevent ovulation." In reality, however, she does admit that meloxicam has "other effects on the conceptus" (Raviele 2014, 127). True, and these effects include abortifacient and teratogenic ones, which are neither medically nor morally acceptable.

Similarly, a mammalian report from Turkey showed that, although meloxicam "is considered to be safe during pregnancy in cattle," its administration to Holstein heifers on day 15 reduces the pregnancy rate from 52 percent (25 of 52 in the control group) to 24.3 percent (9 of 37 in the meloxicam-treated group, $P<0.01$). Because of this proven abortifacient effect in cattle, the researchers suggested, "the use of meloxicam should be avoided if heifers are expected to be pregnant" (Erdem and Guzeloglu 2008).

(3) *Mobic for women*. Raviele also cites a paper from the Croxatto group in further support of her consideration of Mobic as EC for rape (Jesam et al. 2010). Notably, the title of the paper refers to "suppression" of ovulation, not prevention of ovulation.[9]

It is contradictory for Raviele to initially state that meloxicam prevented ovulation (actually delayed or resulted in "dysfunctional ovulation") at rate of 90.9 percent with "no effect on LH, progesterone, estradiol levels or cycle length," then a few paragraphs later state, "one should avoid its use after ovulation, *as it can disrupt survival of the conceptus and implantation*," but ultimately, she still includes the possibility of its usage as EC for rape (emphasis added by Raviele). Raviele, refers to meloxicam as a "highly effective anovulant" (Raviele 2014, 127), but Jesam et al. note that "follicular rupture" occurred in *all* of the [high dose] treatment cycles. Moreover, McCann et al. state plainly enough, "Overall, the data support the concept that meloxicam delays, but does not ultimately prevent ovulation" (McCann et al. 2013). Raviele's citations simply do not support her claim that meloxicam is a "highly effective anovulant."

Moreover, is a 9.1 percent risk acceptable? This is akin to a mother accepting a 9.1 percent risk of death from an antibiotic for her child. Would a physician accept this risk for his or her child? Would any physician consider this risk evidence of "absolute protection"? A breakthrough ovulation rate of 9.1 percent is significant, considering we are dealing with human lives. Moreover, the

McCann et al. study suggests that the rate of breakthrough ovulations is substantially higher than 9.1 percent at a rate of at least 20 percent (i.e., 1–0.80, as their meloxicam-EC efficacy is stated to be 80 percent) (McCann et al. 2013). Simply stated, a pregnancy requires ovulation, and an EC "efficacy" rate of 80 percent can only occur if there is at least a 20 percent breakthrough ovulation rate.

Furthermore, Raviele goes on to imply that NSAIDs are routinely taken by pregnant women 2 weeks after ovulation without concern for adverse effects. In contrast, the previously cited May 2014 report by Harvard rheumatologist, Bonnie Bermas, warns that NSAIDs "should be avoided during a conception cycle so as not to impede implantation." This caution is in addition to the above discussion by Bermas of NSAID-associated fetal anomalies (Bermas 2014).

Raviele's statement, that "Timing is everything!" when administering LNG, should also apply to the NSAIDs. If a matter of few days is crucial relative to the action of LNG, why is it any different for meloxicam, with its known contragestive (abortifacient) effect? Again, an NSAID induced abortion is not a "spontaneous" abortion (Nakhai-Pour et al. 2011), but evidence of lethal risk to the embryo. The uncertainty of cycle date determination in the emergency department (ED) adds greatly to the risk to the embryo.

The emerging role of micro-RNA (miRNA) in early pregnancy is adding to the understanding of embryo risk. A recent Chinese review of miRNA has stated, "The implantation of the blastocyst into the uterus is one of the most critical steps in human reproduction" (Sun et al. 2014). These "miRNAs are emerging as a group of gene-expression modulators critically involved in embryo implantation." The complex mechanisms by which the embryo implants embryoblast pole forward 6 days after fertilization ("day 20 of a 28-day menstrual cycle"; Moore and Persaud 2008) are the subject of intense research. Sun et al. note that COX2-derived prostaglandin E_2 (PGE_2) is considered one the most important signaling molecules for the initiation and progression of embryo implantation" (Sun et al. 2014). Moreover, "In humans, exposure to non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit cyclooxygenases, during pregnancy especially at the time of conception, is associated with over 80 percent increased risk of miscarriage." A drug induced pregnancy loss is, in fact, a medical abortion. Sun et al. also note that "COX2 upregulation leads to PGE2 production and release, which is essential for stromal decidualization and embryo implantation" (Sun et al. 2014).

In arguing for the safety of meloxicam, it is inappropriate to compare women who take this drug for 5 days during the late follicular phase and early luteal phase with women who are in the mid-trimester. The known pharmacology of prostaglandins demonstrates that the risk to the preimplantation embryo in these two groups of women is not similar.

Birth defects, including serious facial and ocular abnormalities, have been reported with first-trimester administration of NSAIDs.[10] If meloxicam were to be used for EC, it is reasonable to expect that EC "failures" (6.5%, as reported by McCann et al. 2013) would be surgically aborted as has been uniformly done with LNG.[11]

(4) *Mobic risks*. Another reason for our opposition to the use of meloxicam for EC comes from the *Physician Desk Reference* (*PDR*). It states that there is "embryolethality" in the rabbit, and an increased incidence of "stillbirths was observed in the rat."

According to the PDR, usage in pregnancy is Category C, before 30 weeks gestation (PDR 2000, s.v. Mobic).

Additionally, the 2011 9th edition of the 2100+ page reference, *Drugs in Pregnancy and Lactation*, states that "human data suggest a risk in the 1st and 3rd trimester of pregnancy with the use of meloxicam" (Briggs et al. 2011). This reference also recognizes a "small" risk of "spontaneous abortions and congenital malformations." Lastly, this authoritative text warns, "Women attempting to conceive should not use any prostaglandin synthesis inhibitor including meloxicam, *because of the finding in a variety of animal models, that these agents block blastocyst implantation*" (emphasis added; Briggs et al. 2011).

The blocking of blastocyst implantation results in the loss of a human embryonic life, via an interceptive (or contragestive) abortion. Furthermore, and as will be discussed in the next section, the clinical uncertainty, relative to the ED treatment of an alleged rape case is substantial. Mobic avoidance appears to be sound clinical advice to assure absolute protection for an early (and vulnerable) embryonic life, and for the pregnant (or possibly pregnant) woman, as well as for their physician.

(5) *EC in the ED–Clinical confusion.* The early major justification for EC was its use with rape/sexual assault victims, but the allegation may be false and the risk of pregnancy, once considered remote, is now thought to be 5 percent.[12] Nonetheless, the circumstances of the conception do not change the inherent dignity of this new life.

There is ED clinical uncertainty as to the presence of an early pregnancy. As noted in note 1 below, a simple urinary pregnancy test provides no information relative to the presence or absence of a rape-induced pregnancy at 72 hours post-coitus. EC researchers studying the drug Ella tested for pregnancy, an EC failure, at 3 weeks, not 3 days (Crenin et al. 2006).

There is also clinical uncertainty as to the determination of the menstrual-cycle day of the patient. Such uncertainty resulted in the previously cited retrospective, group reassignments by Durand et al. Results of a single set of laboratory determinations of a serum LH and progesterone levels, as suggested by Raviele, will not be immediately available to the ED physician. In fact, the progesterone that is submitted in a local 476-bed hospital laboratory on Friday night, will not be available during the Plan B 72-hour window. The serum progesterone result will not be available until the following Tuesday (Saint Joseph Hospital 2007).[13] And, as discussed in note 1 below, its interpretation is clinically problematic.

Moreover, a "substantial discord between the determination of stages of cycle from endocrine data," when compared to "self-report" has been found (Novikova et al. 2007). Novikova et al. reported that only 23 percent of women who were in the peri-ovulatory phase, as determined by serial TVU (transvaginal ultrasonographic) exams, and serial and multiple endocrine data (both "costly"), self-reported this stage (Novikova et al. 2007). Of 41 women in the follicular phase, only 39 percent were correct in their personal estimation (Novikova et al. 2007). Likewise, Noé et al. employed similar serial TVU exams, coupled with serial and multiple hormone measurements, and found that the results differed substantially from the patient's "historical data." These researchers admit to using "provisional" menstrual dating, and stated that, "the day of unprotected intercourse and the day of LNG-EC in relation to ovulation were calculated retrospectively" (Noé et al. 2010). Thus, not even EC experts are able to accurately determine the clinically relevant EC

timing issues rapidly, inexpensively, or simply (Durand et al. 2001; Noé et al. 2010; Novikova et al. 2007).

Remarkably, Muller, Llados, and Croxatto concede this *EC in the ED* clinical uncertainty.[14] With embryological accuracy they observe, "a new human life begins at the time that fertilization is completed. Accordingly, interference with postfertilization events would lead to loss of human life" (Muller, Llados, and Croxatto 2003). It is noteworthy that these authors do not use the "politically correct," but unscientific expected phrase "some *believe* that life begins at fertilization."

Furthermore, this Croxatto-led research team transparently concedes: "When a woman uses EC she does not know whether she takes the pills before or after ovulation and before or after fertilization" (Muller, Llados, and Croxatto 2003). These researchers are indeed right in this assessment, and neither does a prescribing ED physician, a dispensing, assisting, or simply staffing pharmacist (as Plan B is now available OTC and without age restriction), or an approving bioethicist know the precise timing of the EC ingestion, relative to these important life events. All, including the patient/purchaser are truly shooting (or condoning shooting) in the dark.

The physician, who would prescribe Mobic (meloxicam), does not know if ovulation will be prevented, delayed, or neither, or whether the action will be an abortion. Again, Jesam et al. of the Croxatto team found that all women given meloxicam eventually ovulated in the one cycle under study (Jesam et al. 2010).

The ED physician does not know if there will be another act of same-cycle coitus, or multiple such acts. Multiple coital acts have been reported in EC research from the earliest days. The rate of such coital acts that violated research protocol was 19 percent in one early WHO "post-ovulatory" study (Ho and Kwan 1993). The risk of EC "failures" (i.e., pregnancies) is much higher when multiple same-cycle coital acts occur. With LNG-EC now available OTC to children, no interaction with the pharmacist is required and the opportunity for a professional warning against same-cycle, further coital acts is eliminated.

The clinical application of McCann et al.'s report on meloxicam-EC for monkeys is quite doubtful. In fact, these researchers concede, "In the present study, intercourse occurred during a restricted interval within the fertile period." Moreover, McCann et al. restricted the monkeys (Cynomolgus macaques) to a single coital act and daily hormone levels were available for timing of the meloxicam-EC. The co-caged monkey couple was immediately separated after a single visually confirmed coital act. McCann et al. refer to their proposal as "our emergency contraception model." Theirs is indeed a controlled model, unlike the occurrence of rape and its treatment. This laboratory-induced, strict control of subsequent coital behavior, and wealth of multi-day and multi-hormone data is hardly reflective of the real-world environment for the MD in the ED who is considering the urgent administration of meloxicam, LNG, or RU-486.

The previously noted WHO study found that the average day of coitus was approximately the day of ovulation, and the average person received EC 22.5 hours post-coitus. Thus, the majority of subjects were postovulatory (and post-fertilization) (Ho and Kwan 1993).

Meloxicam does not reliably prevent ovulation (McCann et al. 2013). It does, however, block the COX2 receptor that has a central role in conception,

implantation, and decidualization. Meloxicam is given for 5 days and has a long half-life of 20 to 24 hours (Davies and Skjodt 1999). As implantation occurs 6 days after fertilization (day 20 of a 28-day cycle; Moore and Persaud 2008, 38), the embryo is exposed to a potentially lethal threat.[15]

We do not believe that use of meloxicam, as so-called EC, is consistent with the call in the *Catechism of the Catholic Church* for the *absolute protection* of the human embryo "from the moment of conception."[16] The use of a drug with a known ability to end an early pregnancy, and increase the risk of fetal anomalies, appears to fall well below this absolute standard of protection.

Raviele quotes the papally approved instruction *Dignitas personae*, which was released by the Congregation for the Doctrine of the Faith on the Feast of Our Lady of Guadalupe in 2008 (CDF 2008, n. 23).[17] The instruction correctly refers to EC as a prohibited "*interceptive*," and states that one who "requests or prescribes such a pharmaceutical *generally intends an abortion*" (emphasis added by Raviele; Raviele 2014, 125).

St. John Paul II, in *The Gospel of Life*, proclaimed that physicians, and other healthcare workers, have the "inescapable responsibility of choosing to be unconditionally pro-life" (John Paul II 1995, n. 28). Is there a single shred of evidence that St. John Paul II ever approved, or would have approved, any so-called EC in any situation?

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NOTES

1 Strong ethical solidarity with Raviele's primary conclusion of the ethical impermissibility of Plan B does not equate to support for every point made in her paper. Reservations include, but are not limited to, her reference to performing a "pregnancy test to make sure the woman is not pregnant from an act of intercourse two weeks or more before the assault" (Raviele 2014, 118, last paragraph). While we agree that no pregnancy test can detect pregnancy within 72 hours of coitus, and that testing at 3 weeks after midcycle coitus, not 3 days, is standard, she herself quotes on p. 117 the *Ethical and Religious Directives for Catholic Health Care Services* that specifically refer to "a potential conception from the assault. If, after appropriate testing, there is no evidence that conception has already occurred." Is the pregnancy test before EC sound science and how is a negative result customarily explained to the patient?

Additionally, she states, "Any drug which could disrupt a previous implanted embryo would be *abortifacient*" (Raviele 2014, 120). As explained in note 3 below baboon researches established decades ago that Plan B (levonorgestrel) is an interceptive. We trust that Dr. Raviele agrees that life and pregnancy begin with conception (fertilization), and that whether the mechanism of action is interceptive (before implantation) or contragestive (after implantation) the agent is an

abortifacient.

Similarly, and pertinent to this point, she quotes extensively from *Dignitas personae* on p. 125 of her paper (including the critical sentence—who ever "prescribes such a pharmaceutical, generally intends an abortion"), but omits the relevant quote in footnote 43, "The interceptive methods which are best known are the IUD (intrauterine device) and the so-called 'morning after pills'" (CDF 2008).

Likewise, Raviele states, "Secondly, he [Sulmasy] proposes that that the administration of contraceptive hormones *is not intrinsically evil* because they are given for other disorders in women" (Raviele 2014, 126). This statement is partially correct, but the prescription of the birth control pill, a known WHO Group 1 carcinogen —same category as asbestos and arsenic —to a child or a young girl for a non-lethal condition such as acne, and without informed consent to her and a parent/guardian is indefensible medically, ethically and legally (Schneider et al. 2014).

Raviele properly takes further issue with Sulmasy's assertion that contraceptives are *given for other disorders in women*, "This is an incorrect conclusion as the dosage of LNG-EC is equivalent to 50 'mini-pills' of a progesterone-only oral contraceptive and is not physiologic." Raviele is right that Plan B is equivalent to 50 mini-pills, but *levonorgestrel is not progesterone* (the hormone critical to embryo implantation and maintenance of pregnancy). It is a progestin, an anti-fertility agent. A review succinctly summarizes, "Progestins have been used for contraception for more than 30 years" (Erkkola and Landgren 2005). Similarly, Speroff and Darney's contraception text notes that when LNG is administered as the progestin-only Minipill, "Approximately, 40% of patients ovulate normally," and, rather than becoming more receptive, "the endometrium involutes and becomes hostile to implantation" (Speroff and Darney 2006). Plan B is a massive hormonal dose of a sex steroid (the equivalent of 50 mini-pills whose anti-fertility hormone, levonorgestrel, is 200 times as potent at progesterone). The action of Plan B is not that of progesterone, but the opposite of progesterone in action and risk (Schneider et al. 2014). Progesterone is used for luteal supplementation and the reversal of the first step of RU-486 (the administration of mifepristone) (Delgado and Davenport 2012). Plan B is a potent anti-fertility drug that is available to children.

Finally, Raviele states, in a discussion of the Peoria protocol, that if the "serum progesterone level is between 1.5 and 5.9 ng/ml, then she is near ovulation and LNG-EC should not be given" (Raviele 2014, 119). A full discussion of the Peoria protocol deserves a separate paper, but a few comments are perhaps needed here. The protocol has been neither standardized nor validated. A PubMed search located no citations other than Raviele's report. The use of meloxicam with the protocol in women would be a novel application.

Even if a stat progesterone level could be obtained rapidly in the ED, its interpretation is uncertain. The 2012–2015 LabCorp manual states that the progesterone level during the follicular phase is (0.2–1.4 ng/ml)—outside of Raviele's range for "near ovulation" (1.5–5.9 ng/ml). Moreover, the phases in the Labcorp manual are not defined by cycle day and there is overlap in the ranges between the follicular and ovulation phases (0.2–1.5 vs. 0.8–3.0 ng/ml), as well as the ovulation and luteal phases (0.8–3.0 vs. 1.7–27.0 ng/ml) (Labcorp 2012, 686). A single progesterone level, even if obtained rapidly, does not allow the ED physician to know precisely the day of the menstrual cycle and even the menstrual phase.

The 23rd edition of the *Williams* textbook of Obstetrics is 1385 pages in length, but contains only a single paragraph on progesterone and no cycle day information (Cunningham et al. 2010, 41). Similarly, the six volume *Gynecology and Obstetrics* contains a chart on plasma progesterone by week of pregnancy that provides no data prior to the fifth week (Pepe and Albrecht 2003, no. 38, chart on p. 15).

Moreover, Baird et al. studied progesterone levels in early pregnancy as reflected in its major urinary metabolite, pregnanediol-3-glucuronide (PdG). When PdG data are analyzed by day of implantation, the average PdG concentration "increased significantly on the day after implantation (*P*, 0.001)" and "continued to increase gradually during the first week after implantation. The gradual increase in mean PdG concentration after implantation suggests that humans do not exhibit the abrupt rise in progesterone described for nonhuman primates" (Baird et al. 2002). EC researchers, even when armed with multi-day and multi-modality testing including ultra-sound are often in error in their determination of the coital cycle date (Durand et al. 2001). Given the rudimentary tools available late at night in the ED, precise timing of the cycle date is challenging and probably impossible.

The Pill was approved in 1957 for menstrual irregularities, as fertility was not yet viewed as a disease, but evidence of health. By 1960, the Pill ("Enovid") was FDA approved for "contraception," a stretch of the FDA mandate and authority, as fertility was not yet viewed as a disease. The developers knew that there was an implantation prevention ("interceptive" or abortifacient) effect, so in 1965 ACOG attempted to re-define life and pregnancy as beginning with implantation.

Thus, the phrase "emergency contraception" is actually a double (and expanding) lie. It is not a pregnancy that is being prevented, but the birth of a baby, by his or her elimination at the pre-implantation embryo stage with traditional strategies such as DES, Yuzpe or Plan B via interceptive abortions (Oettel et al. 1980). Later, EC was expanded to include contragestive abortions via RU-486 or ella taken in the middle to even late embryonic period, or the insertion of an IUD on day 28 (or beyond). Surgical abortions may legally be performed at any time for EC "failures." These expansions stretch the meaning of EC beyond any semblance of coherence. Is there any other clinical situation in which a medical remedy given 3–5 days after diagnosis (and beyond) is referred to (and properly coded) as "emergency" treatment?

2 Durand et al.'s Table 2 says that follicular rupture occurred on day 18 in group A. If this is considered day 0 and one counts back to "day 10" (i.e., 0, –1, –2, …, –8), one concludes that Durand's "day 10" is eight days before ovulation or day –8 (Durand et al. 2001).

3 Logically it is, of course, impossible to prevent something after it already exists. The Russian baboon researchers were much more forthcoming (and scientifically precise) about the LNG mechanism of action. They noted, "Among primates the baboon is one of the best available species as a model for human implantation.…It has been demonstrated that post-coital levonorgestrel has a good interceptive effect in women" (Oettel et al. 1980).

4 See note 3 above.

5 The major justifications for over-the-counter (OTC) EC were the multiple predictions that easy EC availability would greatly reduce abortions. For instance, Anna Glasier wrote in the *New England Journal of Medicine* that, "each year the widespread use of EC in the United States could prevent over 1 million abortions and 2 million unintended pregnancies" (Glasier 1997).

Although the claim was demonstrably impossible, as there were a total of 848,163 reported U.S. abortions in 2003 (Strauss et al. 2006), the claim went unopposed. It was repeated with increasing frequency and was simply assumed to be true. Nonetheless, after multiple studies failed to find the anticipated benefit of reduced abortions, two meta-analyses were conducted. Both reached the same conclusion that ease of access to LNG, the sole ingredient of Plan B, did not reduce pregnancy rates (Raymond, Trussell, and Polis 2007; Polis et al. 2007). One included report in these meta-analyses, coauthored by the very same Anna Glasier who had predicted an enormous reduction in abortions with OTC EC, provided a quite revealing title, "Advanced provision of emergency contraception to postnatal women in China makes no difference in abortion rates: a randomized control trial"

(Hu et al. 2005). Zero ("no") is certainly less than a million.

In contrast to the Plan B "as soon as possible" efficacy recommendation in a prominent *Journal of the American Medical Association* commentary (Davidoff and Trussell 2006), one of these meta-analyses found advanced provision of EC was associated with "increased use," "multiple use," and "faster use," but did not result in a change of pregnancy rate (Polis et al. 2007). In early 2006, Anna Glasier herself co-authored an editorial in the journal *Contraception* that provided the rather blunt concession, "randomized trials of advanced provision of EC in a variety of settings have all demonstrated increased use of EC, but *none* has shown a reduction in unintended pregnancies" (emphasis added) (Glasier and Shields 2006).

6 "All the patients requested termination of pregnancies, which were confirmed histologically" (Ho and Kwan 1993).

7 An 80% efficacy rate equals 100%* (expected pregnancies - actual pregnancies)/(expected pregnancies) = 100%* (15.18–3)/(15.18) = 80%.

8 *Stedman's Medical Dictionary* defines the term *abortion* as the "1. Expulsion from the uterus of an embryo or fetus before viability (20 weeks gestation [18 weeks after fertilization] or fetal weight less than 500 g)." Thus, a termination of pregnancy before viability, whether via an interceptive, contragestive, or surgical means, does result in an abortion. Moreover, *Stedman's* defines *termination* as an "induced ending of a pregnancy" (Stedman 2006).

9 This Croxatto group report, cited by Raviele, also contains an important admission by these EC researchers/promoters that directly contradicts the position of those promoting the ethical permissibility of Plan B. This report admits that LNG (Plan B) does "suppress the luteal phase," a clear, and authoritatively acknowledged, postfertilization effect (Jesam et al. 2010, postfertilization example 6).

10 As the heart begins to beat on gestational age day 22, it is plausible that on day 20 "the heart, brain, spinal column and nervous system are almost complete and the eyes begin to form" (American Life League 2005). Serious facial and other birth defects have been associated with NSAIDs.

Raviele herself quotes the National Birth Defects Prevention Study (Correa et al. 2012; Hernandez et al. 2012), which found that women exposed to NSAIDs in the first trimester had a "moderate association with anophthalmia/microphthalmia, amniotic bands/limb body wall defects, which had not been reported before, as well as oral clefts" (Raviele 2014, 127).

11 See note 6 above.

12 Holmes et al., as does Raviele, report a rape-related pregnancy risk of 5%, and that "32% of women who became pregnant as a result of a rape were not aware of the pregnancy until the second trimester" (Holmes et al. 1996). A DNA paternity study by Holly Hammond et al. of pregnancies alleged to be rape-associated, found that in 60% of cases (6/10), the consensual partner (or even a second consensual partner) was, in fact, the father, rather than the accused rapist (Hammond, Redman, and Caskey 1995).

13 Additional personal communication with laboratory director, J. Wilhelmus, May 15, 2014.

14 An on-line CV states that Dr. H.B. Croxatto is a physician, president of the Chilean Institute for Reproductive Medicine Society since 1985, past recipient (2002) of the Grand Lodge Masonry of Chile nomination for outstanding contribution to freedom of conscience and thinking, and past faculty member of the Pontifical Catholic University of Chile (1961–1998) (Croxatto 2008).

Croxatto was also the first editor for a 2005 symposium/monograph in Berlin, Germany, on new methods of contraception. He alone authored the lead paper on progesterone receptors and "opportunities for contraception." He notes that, "The aim of this workshop is to explore new avenues in contraception based upon direct pharmacological interventions on PR (progesterone receptor)." Croxatto summarized that progesterone "is required for the production of a viable pregnancy" and "is essential for the establishment and maintenance of pregnancy." The best-known PR blocking agent is the abortion pill, RU-486. In his overview, he offers no ethical hesitation with

this or any of a total of twelve listed "contraceptives," including RU-486 (Croxatto 2005).

15 A recent review of endometrium-embryo cross talk (Banerjee and Fazleabas 2010) refers to this "delicate interaction" as "one of the most elegant and fascinating interactions in human physiology" that "initiates and maintains the process of implantation." The "discourse" is initiated by the pre-implantation blastocyst. Chorionic gonadotropin (CG) signals the corpus luteum, and thus prevents luteal involution and loss of progesterone, that maintains a receptive endometrial lining that is critical to implantation. Moreover, CG signals the endometrium for implantation, and it "rescues stromal fibroblasts from their apoptotic demise and also differentiates them into the decidualized phenotype" (Banerjee and Fazleabas 2010).

16 "Human *life must be respected and protected absolutely from the moment of conception*" (emphasis added) (Catechism 1997, n. 2270).

17 This document (CDF 2008) must have had special relevance to the pope, because at the historic July 10, 2009, meeting between the Supreme Pontiff, now Pope-Emeritus Benedict XVI, and President Barack Obama, there was an unnamed gift. In a surprise gesture, as the president was departing, Pope Benedict gave the American leader a copy of *Dignitas personae* (Moynihan 2009).

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